CHAPTER 2

Behavioural neurotoxicology

Wekking EM, van Hout MSE, van der Laan G
In: Deelman B, Eling P, de Haan E, van Zomeren E (eds):
Klinische neuropsychologie. Amsterdam, Boom, 2004, pp 462-481 (in Dutch)

CHAPTER 2: *Behavioural neurotoxicology*

2.1. Introduction

Neurotoxicity is defined as adverse effects on the structure or functioning of the central and/or peripheral nervous system that result from exposure to chemical substances. Hundreds of organic substances and synthetic products are toxic to humans. The likelihood of damage to the nervous system is determined by the extent of exposure and the toxicity of the substance, which in turn is determined by the ability of that substance to pass the blood-brain barrier and the irreversibility of its effects.

The adverse effects of many neurotoxic substances are often detected when functional disorders of a specific part of the nervous system become manifest. Some neurotoxic substances preferentially affect the central nervous system (CNS), others the peripheral nervous system, and yet others specific cranial nerves. The autonomous nervous system can also be affected. Neurotoxic substances affect the nervous system in different ways, and it is not yet possible to classify these substances on the basis of how they act.

In this chapter a number of neuropsychologically relevant effects of occupational exposure to neurotoxic substances are described in relation to diagnosis and treatment. The neurocognitive effects of alcohol abuse are also described. For the effects of other neurotoxic substances and a large group of pharmaceutical drugs and organic substances, we refer readers to the standard work by Spencer et al. [1]. There is also a small book in Dutch on this subject, by Bercken et al., which contains a lot of relevant information [2].

2.2. Organic solvents

Organic solvents are liquid hydrocarbons. They have two important characteristics: they are lipophilic (they have an affinity for, and can dissolve, fats) and are often highly volatile. They are used for all substances that cannot be dissolved in water, and as such are used for degreasing, cleaning, and dissolving substances both in industry and domestically. The concentration of solvents in the air depends on the size of the working area, the ambient temperature, and the

degree of ventilation. In the Netherlands, an estimated 50,000 people are occupationally exposed to organic solvents in the work place [3]. For example, painters, car sprayers, printers, upholsterers, shoemakers, workers in the chemical and electronics industry, dry cleaners, and laboratory staff.

Solvents are inhaled, and to a lesser extent absorbed through the skin and the gastrointestinal tract. Because they are lipophilic, they can easily penetrate through the cell membrane. Solvents are especially absorbed by organs with a high blood perfusion and a high lipid (fat) content, for instance the liver, kidneys and brains. Solvents are excreted through the kidneys or the lungs. The decomposition process is computed in half-lives: the time it takes between the last exposure to the substance and the moment that its concentration has decreased by half. Solvents usually have a short half-life in blood, but a much longer half-life in adipose tissue. For example, toluene has a half-life of 3 hours in blood but 2 or 3 days in adipose tissue. This means that daily exposure to a toxic substance such as toluene continually increases its concentration in adipose tissue. The situation is aggravated by obesity, because the greater quantity of adipose tissue means that more of the substance is taken up, effectively prolonging its half-life. Simultaneous exposure to several solvents, or the combination of exposure and the use of drugs or alcohol can also extend the half-life.

It is likely that there are individual differences in susceptibility to solvents, which may have a basis in genetic and hereditary differences. For instance, the activity of certain biotransformation enzymes may influence the speed at which toxic substances are decomposed. There are indications that patients who have diabetes mellitus, who abuse alcohol, or who previously suffered brain damage are more susceptible to the harmful effects of solvents.

In industry, solvents are often used in mixtures as ingredients for end products, which makes solvent detection difficult. Moreover, the use of mixtures of solvents carries the risk of additional or synergistic toxicity. Research has established that about 850 chemicals have an adverse effect on the nervous system and behaviour. On the basis of this research, statutory maximum acceptable concentrations, or MACs, for solvents in the workplace have been established.

2.2.1 Acute solvent intoxication

Nearly all volatile organic solvents lead to aspecific effects in cases of acute (short term) exposure to high concentrations. Symptoms include drowsiness, light-headedness, dizziness, headaches, and (abnormal) fatigue. In most instances these effects are reversible. However exposure to very

high concentrations can lead to death or serious disorders such as ataxias, polyneuropathy, epileptic insults, and coma [4].

The effects of solvents are similar to the effects of anaesthetics, and some solvents (trichloroethylene, chloroform) are actually used as anaesthetics. Most solvents have an inhibitory effect on the CNS, and high concentrations of solvents seem to have the same effect as barbiturates and alcohol. A number of solvents are also abused because of their narcotic properties. Acute (peak) exposure at the workplace leads to drowsiness, light-headedness, dizziness, headaches, fatigue, and a feeling of sedation. It has been suggested that these complaints are caused by a change in the accessibility of the cell membrane. The lipophilic character of solvents enables them to enter the cell membrane and to change its physical and chemical properties. Although in the past solvents were thought to have a general effect, evidence suggests that specific solvents react with specific receptor systems [5].

2.2.2 Chronic solvent intoxication

The risk of chronic intoxication depends theoretically on the half-life of the solvent. In real-life situations, people are usually exposed to combinations of solvents, which may have different synergistic and antagonistic effects. Different solvents may affect different brain structures. It has been reported that trichloroethylene affects frontal temporal structures and that carbon sulphide (CS_2) primarily affects sub-cortical structures (basal ganglia) (see table 1). A reliable assessment of the possible effects is only feasible when it is known which solvents are involved and the specific and non-specific effects and possible interactions of these solvents. In reality, this is hardly ever possible. It is for this reason that any statement about the underlying neurological degeneration is considered premature [6].

Since the 1970s, and initially especially in the Scandinavian countries, there have been a large number of studies showing a relation between chronic exposure and neurasthenic and cognitive complaints. However, these results have only partly been confirmed. Differences in research design, methodology (whether or not psychometric tests were used for example), type of solvents, and the extent of exposure make it difficult to compare studies. Moreover, a distinction must be made between epidemiological and clinical studies. Epidemiological studies focus on the correlation between exposure on the one hand and neurological, neurophysiological, or neuropsychological defects on the other. Clinical studies focus on a

Table 1: Solvent exposures and associated disorders [8, 9, 10].

NEUROTOXIN	SOURCE OF EXPOSURE	NEUROLOGIC/NEUROPSYCHIATRIC SYMTOMS
Carbondisulfide	Preservatives, varnishes, viscose rayon, textiles, rubber cement, electroplating industry	Nystagmus, colour-blindness, parkinsonism, psychosis, polyneuropathy, depression, personality change, insomnia, encephalopathy ↓ Eye hand coordination ↓ Psychomotor performance ↓ Reaction time
Ethylene glycol	Coolant, anti-freeze	Fatigue, personality change, depression, nystagmus
Trichloroethylene	Paints, degreasers, dry cleaning industry	Headaches, dizziness, fatigue, diplopia, alcohol intolerance, neurasthenia, anxiety, lability, insomnia, trigeminus neuropathy, encephalopathy ↓ Concentration and memory ↓ Reaction time ↓ Manual dexterity
Perchloroethylene	Paints, degreasers, dry cleaning industry	Encephalopathy, peripheral neuropathy, personality change ↓ Memory ↓ Reaction time
Methyl ethyl ketone (MEK) en methyl-N-butyl ketone	Lacquers, resins, glues, adhesives, inks	Encephalopathy, polyneuropathy, pyramidal symptoms, personality change, depression
Toluene	Glues, benzine, lacquers, thinner	(Leuco)encephalopathy, ataxia, apathy, euphoria, disinhibition, tremor, hearing loss ↓ Memory and attention ↓ Performance IQ ↓ Motor control ↓Visuospatial function
N-hexane	Paints, lacquers, varnishes, inks, glues	Headaches, appetite loss, depression, euphoria, polyneuropathy
Styrene	Polyester, plastics	Encephalopathy, giddiness, dizziness, fatigue, depression, euphoria ↓ Memory and concentration ↓ Psychomotor speed ↓ Reaction time ↓ Vigilance ↓ Visuoconstruction
Xylene	Resins, inks, glues	Encephalopathy, confusion ↓ Reaction time ↓ Attention, ↓ concentration
Methanol	Pigments, anti-freeze, linoleum, paints	Epileptic attacks, confusion, dysarthria
Chloromethane	Degreasers	Euphoria, depression confusion, ↓ Reaction time

group of patients with complaints allegedly related to exposure. A recently published report by Spurgeon offers a summary of a number of epidemiological studies of the effects of long-term exposure to low solvent concentrations on cognitive functioning [7]. Spurgeon meticulously studied the methodological quality of the relevant studies, using criteria that were formulated beforehand, focusing on the clinical relevance and the relation between severity of exposure and performance on neuropsychological tests (the so-called dose-response relation). In 32 of the 45 studies (about 70%) a statistical difference was reported on one or more neuropsychological tests between exposed subjects and unexposed controls. Seventeen of the studies reporting statistical differences also found a dose-response relation. The studies differed strongly in the selection of neuropsychological tests, and certain tests were often used in one study only, which is probably why no neuropsychological pattern of deficits could be detected. Nor is it clear whether the reported statistical differences between patients and controls were due to a remarkably low performance of a small subpopulation of patients or to a slight decrease in the cognitive functioning of the entire exposed group, which may be statistically significant but not very relevant in clinical terms.

2.2.3 Chronic toxic encephalopathy

A small proportion of workers who are occupationally exposed to neurotoxic substances for many years report symptoms of fatigue, headaches, irritability, depression, mental slowness, and memory and concentration problems after many years of exposure. This pattern of symptoms, which is ascribed to long-term exposure, has been given different names over the years: painters' disease, psycho-organic syndrome (POS), and solvent-induced chronic toxic encephalopathy (SCE). In the Netherlands, OPS (organic psycho-syndrome) has become the most familiar term in the media and is used by patient organisations. We prefer the term CTE, because it refers to the exposure to neurotoxic substances as an aetiological factor, to the organic disorders, and to the chronic nature of the disease. When it is restricted to solvent intoxication, the term SCE can be used. About 50 patients are diagnosed with CTE annually in the Netherlands.

It is as yet unclear which factors affect the development and course of the symptomatology. Apart from the degree of exposure, other possible factors are individual susceptibility; the degree of physical exertion at the time of exposure (the implication being that exertion requires a higher use of oxygen, and subsequently a higher intake of toxicants); the (non-) use

Table 2: Diagnostic classification of chronic toxic encephalopathy [6, 11, 12].

Type	Terminology		Symptoms	Reversibility
Type 1	Organic affective or neurasthenic syndrome		Depression, irritability, fatigue, anxiety	Completely reversible in absence of exposure
Type 2	Mild CTE	Type 2 A	Fatigue, mood disturbance, cognitive complaints	Improvement may occur in absence of exposure but permanent mild cognitive deficits can be seen
		Type 2 B	Fatigue, mood disturbance, cognitive complaints, character changes, cognitive deficits on neuropsychological tests (attentional impairment, motor slowing or incoordination, visuospatial deficits, short-term memory loss)	
Type 3	Severe CTE		Cognitive and affective change sufficient to interfere with daily living. Cognitive deficits: see above, more severe. Neurological deficits: abnormalities seen on some neurophysiological or neuroradiological measures.	Irreversible cognitive dysfunction

of protection material; the possible cumulative or interactive effect of exposure to mixtures of (solvent) toxicants; (non-) occurrence of acute intoxication (peak exposure); interaction with alcohol use; the influence of social-emotional problems; and the quality of the social network. International criteria have been developed for the diagnosis of CTE [11, 12] (See Table 2). This diagnostic classification is based on whether the symptoms are reversible and on the nature of the symptoms, which are classified on a continuum, from mild to serious, from reversible to irreversible. However, these criteria appear not to be applied in a uniform way, not even within the EU [13,14]. At present there are initiatives at an international level to develop uniform criteria, which are more useful in clinical practice.

Four conditions must be fulfilled for the diagnosis of CTE: 1) a relevant pattern of complaints, 2) substantial exposure, 3) a plausible relation in time between exposure and complaints, and 4) the exclusion of other obvious explanations for the complaints. In clinical practice, severe CTE is only observed in cases of abuse and very serious accidents. As the pattern of complaints in the organic affective or neurasthenic syndrome is rather non-specific, the focus in clinical practice is primarily concerned with mild CTE, type 2A and 2B. CTE is diagnosed by exclusion

of other possible explanations for the symptoms and diagnosis is usually carried out by a multidisciplinary team, consisting of neurologists, neuropsychologists, occupational physicians and toxicologists. Neuropsychological testing is an essential part of the diagnostic work-up.

The differential diagnosis of CTE is often difficult. There are neurological disorders with overlapping symptoms and defects, such as vitamin deficiencies (B1 and B12), hypothyroidism, the sleep-apnoea syndrome, multiple sclerosis, and cerebral vascular dementia [6]. Alcohol and drug abuse and (side-) effects of drugs can influence neuropsychological test results, as well as premorbid learning and attention problems. Some patients have depressive complaints and in these cases it is difficult to decide whether the complaints give rise to the cognitive defects, or whether the cognitive defects give rise to the depressive complaints. Moreover, many patients are involved in procedures for an assessment of occupational disability or are suing their former employer for liability, which can adversely affect performance during neuropsychological testing [15].

2.2.4. Neuropsychological disorders associated with CTE

In 1986 the WHO established a core battery of neuropsychological tests for the assessment of the cognitive effects of long-term exposure to solvents [16]. It is advisable to include tests of psychomotor speed, reaction time, attention, and memory because these aspects underlie the most frequent complaints of patients with CTE. A computerised test battery has been developed for patients with suspected CTE [Neurobehavioral Evaluation System: NES; 17], which was adapted for the Dutch population and standardised in a representative reference population [18]. The test battery assesses the cognitive and fine motor skills that are often distorted in CTE. This battery is used as a screening instrument by the Dutch Solvent Teams, the two specialised centres for CTE diagnostics in the Netherlands. However, other comparable computerised test batteries can replace this battery. For an adequate assessment of the relevant cognitive skills, this automated test battery needs to be supplemented with memory tests (e.g. CVLT or AVLT, Figural Memory subtest from WMS®III, Rivermead Stories), attention tests (e.g. Stroop Test, Trail Making Test), verbal and non-verbal abstraction tests (WAIS-II Similarities and Block Design), and visual spatial tests (e.g. Rey Complex Figure Test).

It must be acknowledged that this population may show a diminished motivation to perform well, and for this reason tests of malingering should also be administered. Because the

general well-being is often low and mood disorders often occur, it may be sensible to administer one or more symptom checklists [e.g. the Symptom Checklist SCL-90; 19] or specific depression questionnaires/interviews [e.g. Beck Depression Inventory, BDI-II; 20, 21; Structured Clinical Interview for Axis I Disorders (SCID-I); 22, 23].

2.3. Pesticides

Pesticides, which are often used in agriculture to fight weeds, insects, and mould and to increase crop productivity, can be subdivided in organophosphates, chlorated hydrocarbons (e.g. Lindane), and carbamates (e.g. Daigon). Pesticides are used for their toxic effect, and it is thus not surprising that they are also toxic to humans.

Exposure to agricultural pesticides takes place while mixing, loading, and spraying them, but also while working in treated fields, for instance at harvesting time. Exposure usually occurs through skin contact and breathing. Oral exposure can take place because of poor hygiene (smoking and eating with dirty hands), but also by swallowing inhaled particles. The seriousness of exposure depends on the type of work, the way it is carried out (when the field is worked after the pesticide treatment, the type of work carried out), the properties of the pesticide, the crop that has been treated, and also fairly uncontrollable factors like the weather. Various studies have shown that exposure to high doses of pesticides can lead to health risks, such as distorted motor skills, decreased intellectual functioning, and memory problems.

Exposure to organophosphates or carbonates leads to inhibition of acetylcholinesterases. Acute exposure to organophosphates can lead to peripheral neuropathy [24] whereas chronic exposure is associated with problems in sustained attention and speed of information processing [25]. Long-term low-dose exposure to Lindane has been reported to lead to subtle problems in the (working) memory [26,27].

In France, Baldi et al. [28] examined the cognitive functioning of 917 vineyard workers and related this to their exposure to pesticides (fungicides) over the years. Those who had been directly and indirectly exposed had a worse performance on tests of memory, selective attention, verbal fluency, and verbal abstraction, compared with non-exposed individuals. Exposed subjects were slower on tests of selective attention and mental flexibility. When there was no time limit the results were comparable between exposed and non-exposed groups. The study participants symptoms were sub-clinical and did not interfere with the ability to work. In a later study

with a population of 1507 elderly individuals, it was found that a high exposure to pesticides increased the relative risk of Alzheimer and Parkinson diseases [29]. In a comprehensive Dutch study as a sub-section of the 'Maastricht Aging Study', Bosma et al. [30] examined 830 subjects, 629 of whom had been exposed to pesticides in their occupational past. Exposure to pesticides was associated with an increased risk of MCI (Mild Cognitive Impairment).

2.4. Metals

'Heavy metals' are metal elements with a density greater than 8 g/cm^3. The most familiar heavy metals are lead, cadmium, and mercury. Heavy metals enter the body through direct occupational exposure (breathing in, swallowing), but are also ingested in very small quantities in our food.

2.4.1 Lead

The toxicity of lead was recognised in ancient times. Hippocrates described the symptoms of chronic lead poisoning under the name 'Saturnism'. In the last few centuries lead intoxication was a hazard of various occupations: lead miners, lead smelters, printers (lead type) and painters (lead white). Later, people came into contact with lead through canned food and lead water pipes. After World War II lead in gasoline became a growing problem, because of the great increase in the use of cars and other motorised vehicles. The growing awareness of the health risks of exposure to lead has led to measures that have resulted in a strong decrease in the intake of lead in the body. In the workplace, inhalation is the main route of lead intoxication; very little enters the body by the oral route. Burning off old paint layers occasionally leads to lead poisoning. Epidemiological research has established acceptable limits for exposure. The effects of lead poisoning depend on the dose and duration of exposure, and can be subdivided in neurological, haematological, gastrointestinal, cardiovascular, and renal effects; lead also affects fertility. Children are especially vulnerable to exposure of lead. In the beginning, complaints are usually non-specific: fatigue, apathy, diminished appetite, pain in joints and bones. It has been reported that low exposure leads to subtle effects, such as a mild slowing of

neurotransmission [31]. If exposure continues, other symptoms are sleeplessness, confusion as well as concentration and attention problems. Long-term exposure can lead to a distal motor polyneuropathy with extension weakness of the wrist stretchers ('dropping hand'). Only rarely does lead encephalopathy lead to insults and coma [32]. Neuropsychological defects are found in learning, memory domains, attention, visual-spatial information processing, and psychomotor function [33].

2.4.2. Cadmium

Cadmium is widely used in the electronics industry (production of re-chargeable nickel cadmium batteries), in the metal industry (galvanising metal surfaces), and in the manufacturing industries (the colouring of plastics). The dangers of cadmium were recognised only recently, and the regulations governing its application, use, and collection have been sharpened. Cadmium has a long half-life: 15 years. This may easily lead to accumulation of cadmium in the body, especially in the kidneys and liver [34]. High exposure to cadmium can cause bone weakness and skeletal deformation and increase the risk of cancer.

2.4.3. Mercury

In the last centuries mercury poisoning has been described in professions such as mirror makers and milliners. Milliners used mercury to mould felt into the required shape. Prolonged exposure to the mercury vapours caused mercury poisoning. Victims developed severe and uncontrollable muscular tremors and twitching limbs, called "hatter's shakes"; other symptoms included distorted vision and confused speech. Advanced cases developed hallucinations and other psychotic symptoms. The term "Mad Hatter" is popularly recognised from the character described in Alice in Wonderland by Lewis Carroll, but the phrases "mad as a hatter" and "mad as a March hare" were common at the time (1865) Lewis Carroll wrote Alice. In the 1960's, mercury was the focus of media attention as an environmental threat after food scandals in Japan (Minamata), where many people suffered serious neurological disorders and tens of people died after eating (shell) fish harvested from waters contaminated by mercury [34]. Chronic high

exposure to mercury affects the nervous system. Early symptoms are a diminished feeling in the extremities, lips, and tongue. In a further stage tremors and ataxias occur, as well as a decrease in vision and hearing. Micrography is characteristic. In the final stage there is dementia and physical disability. Over the last ten years there is a growing interest in the risks of mercury use in amalgam fillings, for dentists as well as the patients. There is some controversy about this issue [35].

2.5. Carbon monoxide (CO)

In the United States, carbon monoxide (CO) poisoning is the main cause of death due to non-occupational exposure to toxic substances [36]. In the Netherlands, nine people die of CO poisoning every year, and on average 1200 people receive hospital treatment for symptoms of CO poisoning annually. It is possible that many cases of CO poisoning are not diagnosed as such. Poisoning often goes unnoticed because CO is a colourless, tasteless, odourless, and non-irritable gas. It is a product of combustion when there is a deficiency of oxygen and is a metabolite of inhaled methylene chloride. Sources of CO are heating systems, combustion engines in badly ventilated rooms, fire and cigarette smoke (2% to 6% CO). The gas is absorbed quickly by the lungs. CO binds to haemoglobin, resulting in a diminished oxygen-transporting capacity of the blood. This in its turn leads to hypoxia in the brain and to decreased cellular oxygen metabolism, causing tissue damage. It causes acute demyelinisation and damage to sub-cortical white matter, globus pallidus, thalamus and hippocampus, but it also leads to global cortical atrophy.

Acute CO poisoning can lead to breathing problems, loss of consciousness, cognitive disorders, coma, and even death. Even after initial recovery, clinical symptoms may recur at a later stage, including epileptic insults, extra-pyramidal syndrome, cortical blindness, dementia, and behavioural disorders. Cognitive disorders after CO poisoning occur in 30% to 67% of patients [36]. Parkinson and his colleagues [37] found in 30% of the patients with recent CO poisoning defects in executive functioning, mental speed, and visual-spatial skills. Patients who had been unconscious for more than 5 minutes during acute poisoning had a poorer global performance than patients who had been unconscious for less than 5 minutes. The standard treatment for CO poisoning is 100% oxygen or in some cases hyperbaric oxygen (administered under high pressure).

2.6. Alcohol

Alcohol is an organic solvent that - in contrast with the previously discussed neurotoxic agents - is used for human consumption. Alcohol is - like the other solvents - lipophilic and can easily damage the neurons in the brain. Recent results suggest that alcohol stimulates inhibitory neurotransmission and inhibits excitatory neurotransmission [38]. Alcohol has an inhibitory effect on the CNS and is associated with the clinical symptoms of amnesia and ataxia. The reinforcing effect of alcohol is caused by the release of opiates and cannabinoids.

The literature mentions the loss of grey matter through chronic alcoholism in cortical (bilateral; frontal tempo-parietal regions) as well as sub-cortical (diencephalon, nucleus caudatus) structures [39]. White matter defects [40] and specific receptor defects [41] are also mentioned. Sub-cortical pathology has been related to nutritional status and age: bad food habits lead to sub-cortical defects that are more pronounced in older individuals. Chronic alcohol abuse can in some cases lead to a serious deficiency of vitamin B1 (thiamine). If supplements are not administered, such a deficiency can cause death. A serious thiamine deficiency leads to lesions in specific nuclei of the thalamus, the mammillary bodies, and other limbic structures, and defective cholinergic neurotransmission. Magnetic resonance imaging (MRI) shows a loss of cells in the orbitofrontal and mesiotemporal cortex, the thalamus, and other diencephalonic structures as well as enlarged ventricles [42]. It had always been assumed that there are two distinguishable neuropathological processes underlying chronic alcoholism and Wernicke-Korsakoff syndrome (WKS, see next section), but recently this view has become under discussion. MRI studies show that WKS has a more heterogeneous neuropathology than what has always been assumed [43].

2.6.1 Alcohol-related syndromes

In the Netherlands, 10.2% of the adult population are regular drinkers (the limit for women, more than 14 glasses a week; for men more than 21 glasses a week), 4.6% abuse alcohol, and 3.7% meet the DSM criteria of alcohol independence [44].

The DSM-IV distinguishes - apart from alcohol dependence and alcohol abuse - several disorders caused by alcohol, the two most important being persisting amnesia, otherwise known as Wernicke-Korsakoff syndrome (WKS), and persisting dementia due to alcohol abuse.

These two syndromes are serious chronic disorders. Clinical characteristics of WKS are confusion or delirium, abnormal eye movements (ophthalmoplegia, nystagmus), and ataxia. This clinical triad is associated with Wernicke pathology, which develops during a period of extreme alcohol consumption. The symptoms are caused by a serious vitamin B1 deficiency that can even lead to death if this vitamin is not administered in time. Large doses of vitamin B1 resolve the delirium and diminish the ophthalmoplegia and ataxia. What is left are peripheral neuropathy and the amnesia symptoms, which are characteristic for Korsakoff syndrome. In the first stage patients often confabulate. If they are asked about what they did yesterday, they come up with the most eccentric answers. A patient with full-blown Korsakoff syndrome lives in a time zone of 3 to 5 minutes. Other behavioural changes, apart from the cognitive impairments, are apathy, emotional numbness, loss of initiative, and a loss of interest in past, present and future. While the chronic alcoholic can lead a fairly normal life in society, the Korsakoff patient cannot.

There are instruments for screening for alcohol dependence, such as the short self-reporting questionnaires the CAGE [45] and the AUDIT [46]. The standardised psychiatric interviews known as CIDI [47], SCID [23] and MINI [48] contain sub-sections on alcohol use. Other indications can be obtained by looking for alcohol-related biochemical markers in the blood. However, it is advisable to use several instruments or markers in combination. Several studies indicate that the biochemical markers are especially useful in measuring intra-subject variation in drinking behaviour, particularly in cases of decreased alcohol consumption [49]. The clinical course of alcoholism shows that health problems emerge practically always in the same order: head injuries, blackouts, hypertension, diabetes, withdrawal epilepsy, liver dysfunction, and chronic obstructive pulmonitis. It is important for the neuropsychologist to be aware of these somatic problems because they can affect test scores, which means that their effect has to be distinguished from the neurotoxic effects of alcohol.

2.6.2 Neuropsychological defects caused by alcohol use

The following criteria have to be met for the DSM-IV diagnosis of 'alcohol-induced persisting dementia': memory impairment (impaired ability to learn new information or to retrieve previously acquired information) and one or more of the following cognitive disturbances, aphasia (language disturbance), apraxia (impaired ability to carry out motor activities despite intact motor function), agnosia (failure to recognise or identify objects despite intact

sensory function), and one or more disturbances in executive functioning. A great number of serious cognitive deficits are possible, but these disturbances are not to be confused with the characteristic amnesia of Korsakoff syndrome.

In the case of WKS (i.e., alcohol-induced persisting amnesia), the most important cognitive deficit is a serious defect in learning and retrieval of recently acquired information. Characteristic of WKS is the anomaly between global intellectual functioning, which is usually at a premorbid level, and memory function, which is usually dramatically diminished. The memory problems are characterised by anterograde amnesia with a heightened sensitivity to interference, and retrograde amnesia in which a temporal gradient can be detected. It should also be noted that patients with Korsakoff syndrome have great problems in putting events in chronological order. There is no learning curve when Korsakoff patients learn word lists and there are many intrusions and perseverations.

Although most heavy drinkers do not meet the criteria for dependency or abuse, about 50% of the remaining alcoholics have cognitive deficits, which may affect everyday life. Of these, 10% to 30% have permanent cognitive problems even after 1 year of abstinence; the rest of this group have only problems in the periods of alcohol abuse [50]. Most studies have focused on recently detoxified alcoholics, who are mostly white men in their mid-forties with an above-average education who have been heavy drinkers for the last 10 or 20 years. Testing usually takes place 2 or 3 weeks after abstinence to avoid acute withdrawal symptoms. Alcoholics show a typical neurocognitive profile with deficits on tasks requiring problem solving and adaptive behaviour [50]. Deficits are also observed in executive functions, visual-spatial organisation, perceptual-motor integration, and simple motor skills. Only mild disturbances of learning and memory are observed. Verbal skills and general intelligence are usually on a premorbid level.

In order to be able to assess the effects of alcohol abuse on cognitive functioning adequately, the test battery should include tests of (working) memory (especially tests that are good in measuring interference, such as the CVLT and the Rivermead Stories), attention (Stroop Test, Trail Making Test, PASAT), visual-spatial organisation (Complex Figure Test), perceptual-motor integration (Purdue Pegboard, Eye-hand coordination Test), executive functions (Wisconsin Card Sorting, Behavioural Assessment of the Dysexecutive Syndrome (BADS)), and fine motor skills (Finger Tapping).

2.7. Drugs

The acute effects of the various narcotic drugs have been extensively described but much less is known about the long-term neuropsychological effects of drug abuse. Research in this field is complicated because the study population consists of people with a career in poly-drug abuse whose premorbid status is not clear. Selby and Azrin concluded in their study that poly-drug abusers performed worse on tests of short- and long-term memory and on tests of visual motor skills in comparison with age- and education-matched abusers of alcohol or cocaine [51]. Recent literature indicates that extensive use of popular drugs like XTC (ecstasy; 3,4-methylenediox ymetamphetamine; MDMA) can lead to memory defects [52, 53]. A detailed description of the effects of drug abuse is beyond the scope of this chapter. For the effects of various drugs, we refer readers to the relevant chapters on drug abuse by Carlin and O'Malley in Grant and Adams [54] and to Lezak [55].

2.8. Possible treatments

2.8.1 Chronic toxic encephalopathy

The possibilities to treat CTE are limited. The first step is to stop or diminish exposure to neurotoxic substances. As of 1 January 2000, paint and glue used in the painting, parquet and carpet-laying industries should be free of organic solvents in the Netherlands. This legal requirement has since been extended to printing and car-spraying industries.

After cessation of exposure, the pattern of symptoms and complaints is only partially reversible in affected individuals. The somatic treatment of CTE will for the greatest part be symptom oriented (pharmacological): analgesics for headaches and other pain complaints, antidepressives for mood disorders, and anxiolytics for anxiety complaints. Three factors seem to influence the course of CTE: 1) personal factors, such as the severity of the cognitive disorder, the individual coping style, and cognitions about CTE; 2) the social network of the individual (family, work, leisure); and 3) the national infrastructure for prevention, diagnostics, and compensation for occupational disability [56]. A diagnosis of CTE often has a profound influence on the patient's personal life. The need to stop exposure often leads to job loss, disability pensioning, and consequently nearly always financial setbacks. Family tensions often occur because of the patient's increased irritability or emotionality, social activities are usually limited; thereby

making these families more of a closed system, family roles change, and the social network diminishes. As in other chronic diseases, many families are unable to adapt the initial necessary adjustment to acute problems to a role pattern more suitable to the chronic situation. The few studies of the effect of psychological treatment of CTE have tended to concentrate on group treatments for social-emotional problems and cognitive complaints. All of the four available studies reported on small clinical uncontrolled groups of patients [57; chapter 6]. These studies suggested that treatment of CTE should focus on stimulating contact between fellow-patients, social reintegration, relaxation exercises, and cognitive rehabilitation.

2.8.2 Alcohol

There are several specialised regional centres for the treatment of alcohol problems in the Netherlands. They offer (part-time) clinical treatment for both in-patients and out-patients. The essence of the treatment programme is to motivate the person to undergo treatment (many patients do not recognise their addiction), to detoxify if necessary, and to prevent the return to alcohol use. Most treatment programmes consist of several modules centred on information, training social skills, psychomotor therapy, leisure, and relaxation. There are separate male and female groups. Pharmacological treatment can sometimes be indicated, especially when in the past long-term abstinence was not achieved. Drugs such as disulphiram, acomprosate, and naltrexone diminish the craving for alcohol. An out-patient treatment protocol that tackles the alcohol problems with a cognitive-behavioural approach has been described. Its rationale is that drinking behaviour is an acquired habit, which is constantly enforced [58]. The treatment covers how to cope with the craving for alcohol, to learn to endure the absence of alcohol, and to learn how to break out of the expectations about drink and behaviour in social situations. Allen et al questioned the adequacy of the treatment of patients with cognitive defects [59]. It is not clear to what extent the techniques from cognitive rehabilitation are applied in Dutch alcohol programmes.

2.9. Case studies

2.9.1. CTE case study

The subject was a 53-year-old painter with various pain complaints, fatigue, forgetfulness, a decreased sense of smell, and mood complaints. The complaints had been present for 15 years but had gradually become worse. The patient's wife thought that her husband's character had changed over the years. His forgetfulness often gave rise to family arguments. He spent less time on his hobby and social activities, and he had to force himself to go to birthday parties, which he thought were noisy and chaotic, and where he could not follow the conversation. The general practitioner had referred him.

He had been a painter for 30 years. The exposure was assessed to be moderately high by an occupational hygienist. He had been on sick leave for 1 year and his fatigue had diminished in this period. Neurological examination revealed a slight extra-pyramidal disorder. He was not using medication except for painkillers about three times a week. He had completed 7 years of primary education, without staying down; he had difficulty with writing and spelling.

The test results showed defects in reaction (on the simple as well the complex tasks), attention (selective), and memory (verbal and visual, especially imprinting). Verbal and non-verbal abstraction was at a premorbid level. The scores on the malingering tasks did not indicate insufficient effort. Symptom Checklist scores were very high (in comparison with a healthy male reference group) on Insufficiency in thinking and acting, and high on the psycho neuroticism scale, indicating a low level of psychological and somatic well-being. After discussion in a multi-disciplinary team, during which possible differential diagnoses were discussed, it was concluded that the overall picture was consistent with CTE. The patient was advised to minimise exposure permanently. Because of the severity of the patient's complaints, he was given the opportunity to participate in the special group therapy called 'Coping with OPS/CTE'.

2.9.2. Alcohol abuse case study

Subject was a 47-year-old housewife who had had periods of alcohol abuse for more than 15 years. She was married with two children. Her son, a 20-year-old college student, lived on his own, whereas her daughter was 4 four years old and had just entered primary school. Her husband was away from home very often because of his work. Lately, she had started to have blackouts,

which created a precarious situation for her and her daughter (who seemed to be neglected and was not always fed properly). A woman friend of hers had told her husband, who in his turn had put pressure on her to seek professional help.

She was referred to the psychiatric out-patient department, where she underwent neuropsychological and neurological testing. Neurological examination revealed hypertension and mild ataxia. At the neuropsychological examination, she appeared well dressed and looked slightly older than her age. Her walk was slightly unsteady. She seemed to take her alcohol-related complaints lightly, saying that they were the side effects of her medication (anti-depressives prescribed by the general practitioner). She was not really motivated to stop drinking. She did indicate that she was sometimes depressed.

She was motivated and cooperative during neuropsychological testing. Results revealed mild defects in the verbal and visual memory domains, with interference, divided attention, and diminished visual-spatial planning and visual-constructive functions. She had low scores for verbal abstraction, given her educational background (athenaeum / equivalent to grammar school). Speed of information processing and selective attention were undisturbed. It was concluded that she had mild defects, which could be related to chronic periodic alcohol abuse. The results were discussed with the subject. She received medication for hypertension and was asked to participate in the out-patient cognitive behavioural therapy protocol for people with alcohol problems. She did not immediately agree but would consider it.

References

1. Spencer PS, Schaumburg HH: Experimental and clinical neurotoxicology. New York, Oxford University Press, 2000.
2. Bercken JMM, Genderen H van, Vlieger M de: Neurotoxische stoffen. Wageningen, Pudoc, 1986.
3. Hoek JAF van der, Verberk MM, Laan G van der, Hageman G: Solvent-induced chronic encephalopathy; the 'solvent team' project. Ned Tijdschr Geneeskd 2001;145(6):256-260. Review.
4. Houck P, Nebel D, Milham Jr S: Organic solvent encephalopathy; an old hazard revisited. Am J Ind Med 1992; 22:109-115.
5. Arlien-Søborg P: Solvent Neurotoxicity. Boca Raton, CRC Press, 1992.
6. White RF, Proctor SP: Solvents and neurotoxicity. Lancet 1997;349:1239-1243. Review.
7. Spurgeon A: The validity and interpretation of neurobehavioural data obtained in studies to investigate the neurotoxic effects of occupational exposure to mixtures of organic solvents. Birmingham, Health and Safety Executive Contract Research Report 355/2001, 2001.
8. Gans J de, Hageman G: Cerebrale infecties, tumoren en intoxicaties in niet-aangeboren hersenletsel bij volwassenen; in Vermeulen J, Derix MMA, Avezaat CJJ, Mulder Th, Strien JW van (eds): Niet aangeboren hersenletsel bij volwassenen. Maarssen, Elsevier, 2003.
9. Bolla KI, Rocca R: Neuropsychiatric sequelae of occupational exposure to solvents; in Bleecker, ML (ed): Occupational Neurology and clinical neurotoxicology. Baltimore, Williams & Wilkins, 1994, pp. 133-159.
10. Feldman RG: Occupational and Environmental Neurotoxicology. Philadephia, Lippincott-Raven, 1998.
11. WHO and Nordic Council of Ministers Working Group: Chronic effects of organic solvents on the central nervous system and diagnostic criteria. Environ Health 1985;5:20-35.
12. Baker EL, Seppäläinen AM: Workshop on neurobehavioral effects of solvents. Human aspects of solvent neurobehavioral effects. Neurotoxicology 1986;7:45-56.
13. Hoek, JAF van der, Verberk MM, Laan G van der, Hageman G: Routine diagnostic procedures for chronic encephalopathy induced by solvents: survey of experts. Occup Environ Med 2001;58:382-385.
14. Triebig G, Hallerman J: Survey of solvent related chronic encephalopathy as an occupational disease in European countries. Occup Environ Med 2001;58:575-581.
15. Hout MSE van, Schmand B, Wekking EM, Hageman G, Deelman BG: Suboptimal performance on neuropsychological tests in patients with suspected chronic toxic encephalopathy. Neurotoxicology 2003;24:547-551.
16. World Health Organization: Operational guide for the WHO neurobehavioral core test battery. Geneva, WHO Office of Occupational Health, 1986.
17. Baker EL, Letz RE, Fidler A: A computer-administered neurobehavioral evaluation system for occupational and environmental epidemiology. J Occup Med 1985;27:206-212.
18. Emmen HH, Hoogendijk EMG, Hooisma J†, Orlebeke JF, Uitdehage SHJ: Adaptation of two standardized international test batteries for use in the Netherlands for detection of exposure to neurotoxic compounds. Internal Report 1988-18. TNO, Medical Biological Laboratory. Rijswijk, The Netherlands, 1988.
19. Arrindell WA, Ettema JHM: SCL-90, Handleiding bij een multidimensionele psychopathologie indicator. (Dutch manual SCL-90). Lisse, Swets en Zeitlinger, 1986.
20. Beck AT: BDI-II, Beck Depression Inventory: Manual. Harcourt Brace, 2nd ed., 1996.
21. Does AJW van der: Beck Depression Inventory-II. Dutch translation and adaptation. Lisse, Swets Test Publishers, 2003.
22. Spitzer RL, Williams JB, Gibbon M, First MB: The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. Arch Gen Psychiatry 1992;49(8):624-629.
23. Groenestijn MAC van, Akkerhuis GW, Kupka RW, Schneider N, Nolen WA: Gestructureerd klinisch interview voor de vaststelling van DSM-IV As-I stoornissen. Lisse, Swets en Zeitlinger, 1999.

24. Ray DE, Richards PG: The potential for toxic effects of chronic, low-dose exposure to organophosphates. Toxicol Lett 2001;31:343-51.

25. Stephens R, Spurgeon A, Calvert IA, Beach J, Levy LS, Berry H, Harrington JM: Neuropsychological effects of long-term exposure to organophosphates in sheep dip. Lancet 1995;345:1135-1139.

26. Anand M, Agrawal AK, Rehmani BN, Gupta GS, Rana MD, Seth PK: Role of GABA receptor complex in low dose lindane (HCH)induced neurotoxicity: neurobehavioural, neurochemical and electrophysiological studies. Drug Chemical Toxicol 1998;21(1):35-46.

27. Peper M, Ertl M, Gerhard I: Long-term exposure to wood-preserving chemicals containing pentachlorophenol and lindane is related to neurobehavioral performance in women. Am J Ind Med 1999;35:632-641.

28. Baldi I, Filleul L, Mohammed-Brahim B, Fabrigoule C, Dartigues JF, Schwall S, Drevet JP, Salamon R, Brochard P: Neuropsychological effects of long-term exposure to pesticides: results from the French Phytoner study. Environ Health Perspect 2001;109:839-844.

29. Baldi I, Lebailly P, Mohammed-Brahim B, Letenneur L, Dartigues JF, Brochard P: Neurodegenerative diseases and exposure to pesticides in the elderly. Am J Epidemiol 2003;157:409-414.

30. Bosma H, Boxtel MP van, Ponds RW, Houx PJ, Jolles J: Pesticides exposure and risk of mild cognitive dysfunction. Lancet 2000;356:912-913.

31. Landrigan PJ: Lead; in Rosenstock L, Cullen MR (eds): Textbook of Clinical Occupational and Environmental Medicine, 3rd ed. St Louis, M.O., Moshby-Year Book, 1994, pp 745-754.

32. Lewis RL: Metals; in Ladou J (ed): Occupational and Environmental Medicine, 2nd ed. Stamford, C.T.,Appleton and Lange, 1997, pp 405-439.

33. Seeber A, Meyer-Baron M, Schaper M: Summary of two meta-analyses on neurobehavioural effects due to occupational lead exposure. Arch Toxicol 2002;76:137-145.

34. Deelstra H, Massart D, Daenens P, Peteghem C. van: Vreemde stoffen in onze voeding. Monografieën Stichting Leefmilieu. België, Uitgeverij Pelckmans, 1996.

35. Dodes, JE: The amalgam controversy. An evidence-bases analysis. J Am Dent Ass 2001; 132:348-356.

36. Deschamps D, Géraud C, Julien H, Baud FJ, Dally S: Memory one month after acute carbon monoxide intoxication: a prospective study. Occup Environ Med 2003;60:212-216.

37. Parkinson RB, Hopkins RO, Cleavinger HB, Weaver LK, Victoroff J, Foley JF, Bigler ED: White matter hyperintensities and neuropsychological outcome following carbon monoxide poisoning. Neurology 2002;58:1525-1532.

38. Stahl SM: Essential Psychopharmacology. Neuroscientific basis and Practical Application, 2nd ed. Cambridge University Press, 2000.

39. Jernigan TL, Butters N, DiTraglia G, Schafer K, Smith T, Irwin M, Grant I, Schuckit M, Cermak LS: Reduced cerebral grey matter observed in alcoholics using magnetic resonance imaging. Alcohol Clin Exp Res 1991;15:418-427.

40. Jensen GB, Pakkenberg B: Do alcoholics drink their neurons away? Lancet 1993;342:1201-1204.

41. Freund G, Ballinger Jr WE: Loss of synaptic receptors can precede morphologic changes induced by alcoholism. Alcohol Alcohol 1991;1(Suppl):385-391.

42. Jernigan TL, Schafer K, Butters N, Cermak LS: Magnetic resonance imaging of alcoholic Korsakoff patients. Neuropsychopharmacology 1991;4:175-186.

43. Blansjaar BA, Vielvoye GJ, Dijk JG van, Rijnders RJ: Similar brain lesions in alcoholics and Korsakoff patients: MRI, psychometric and clinical findings. Clin Neurol and Neurosurg 1992;94:197-203.

44. Verdurmen J, Monshouwer K, Dorsselaer S van, Graaf SR de: Bovenmatig drinken in Nederland. Achtergrondstudie Nationale Drugmonitor. Trimbos Instituut, 2003.

45. Mayfield D, McLeod G, Hall P: The CAGE questionnaire. Validation of a new alcoholism instrument. Am J Psychiat 1974;131:1121-1123.

46. Saunders JB, Aasland OG, Babor TF, De La Fuente JR, Grant M: Development of the Alcohol Use Disorder Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption. Part II. Addiction 1993;88:791-804.

47. Smitten MH ter, Smeenk RMW, Brink W van der: Composite International Diagnostic Interview (CIDI). Basic version 2.1 Interviewer Manual. World Health Organization, 1997.

48. Vliet IM van, Leroy H, Megen, HJGM van: MINI Plus. MINI International Neuropsychiatric Interview. Dutch version 5.0 Publication Utrecht Medical Center, 2000.

49. Duckert F, Johnsen J, Amundsen A, Stromme J, Morland J: Covariation between biological markers and self-reported alcohol consumption: a two year-study of the relationship between changes in consumption and changes in the biological markers gamma-glutamyl transpeptidase (GGT) and average volume per erythrocyte (MCV) among problem drinkers. Alcohol Alcohol 1992;27:545-555.

50. Rourke SB, Løberg T: The neurobehavioral correlates of alcoholism; in Grant I, Adams KM (Eds): Neuropsychological Assessment of Neuropsychiatric Disorders. New York, Oxford University Press, 1996.

51. Selby MJ, Azrin RL: Neuropsychological functioning in drug abusers. Drug Alcohol Depend 1998; 50:39-45.

52. Reneman L, Lavalaye J, Schmand B, de Wolff FA, van den Brink W, den Heeten GJ, Booij J: Cortical serotonin transporter density and verbal memory in individuals who stopped using 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy"): preliminary findings. Arch Gen Psychiatry 2001;58(10):901-906.

53. Reneman L: Designer drugs: how dangerous are they? J Neural Transm Suppl, 2003;66:61-83. Review.

54. Carlin AS, O'Malley S: Neuropsychological consequences of drug abuse. In: Grant I, Adams KM. Neuropsychological Assessment of Neuropsychiatric Disorders. New York, Oxford University Press, 1996.

55. Lezak MD, Howieson DB, Loring DW: Neuropsychological assesment, 4th edition. New York, Oxford University Press, 2004.

56. Ørbaek P: Solvent-induced disability and recovery after cessation of exposure; in Chang LW, Dyer RS (eds): Handbook of Neurtoxicology. New York, Dekker, 1995, pp 339-354.

57. Hout MSE van, Wekking EM, Berg IJ, Deelman BG: Psychological treatment of patients with chronic toxic encephalopathy: lessons from studies of chronic fatigue and whiplash. Psychother Psychosom 2003;72:235-44.

58. Wildt WAJM de, Schippers GM: Protocollaire behandeling van patiënten met alcoholproblemen. Motivering, zelfcontroletraining en terugvalpreventie; in Keijsers GPJ, Minnen A van, Hoogduin CAL (eds): Protocollaire behandeling van patiënten in de ambulante geestelijke gezondheidszorg. Houten, Bohn Stafleu van Loghum, 1999.

59. Allen DN, Goldstein G, Seaton BE: Cognitive Rehabilitation of chronic alcohol abuse. Neuropsychol Rev 1997;7:21-39.